UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/762,261 | 05/29/2001 | Gerald V. Quinnan JR. | 044508-5001 | 2761 |

9629 7590 03/11/2003

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

| EXAMINER | |
|---|---|
| FOLEY, SHANON A | 15 |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/762,261 | QUINNAN ET AL. | |
| **Office Action Summary** | Examiner | Art Unit | |
| | Shanon Foley | 1648 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**P riod for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23-36* is/are pending in the application.

4a) Of the above claim(s) *25 and 27-29* is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 23* is/are allowed.

6)☒ Claim(s) *24,26 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

In paper no. 12, applicant cancelled claims 3-22 and added new claims 23-36. Claims 2 and 23-36 are pending.

### *Election/Restrictions*

Newly submitted claims 25, 27-29 and 30, 34-36 as far as they depend from claims 25, 27-29, are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 25, 27-29 are drawn to an HIV protein comprising a specific amino acid sequence, SEQ ID NO: 24. The HIV protein of the original elected invention comprises amino acid sequence SEQ ID NO: 1. This specific sequence defines the special technical feature of claim 2 and is shared by the first newly presented claim 23. An HIV protein comprising a different amino acid sequence, i.e. SEQ ID NO: 24, lacks unity of invention with the first group because the residues do not share sequence order, residue structure or molecular weight. In addition, even if the proteins encoded by SEQ ID NO: 24 comprise a portion of SEQ ID NO: 1, the proteins are not required to have other residues in common with SEQ ID NO: 1. Also, the amino acids comprising SEQ ID NO: 24 are not required to be conserved with SEQ ID NO: 1 since any 9 of the 13 amino acids may be conservatively substituted. Therefore, the HIV proteins comprising a different sequence from an HIV protein consisting of amino acid sequence SEQ ID NO: 1, lacks unity of invention with the first group.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 25, 27-29 and 30, 34-36 as they depend from claims 25, 27-

29 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to an isolated HIV envelope protein having at least 95% to 99% sequence identity to the polypeptide encoding SEQ ID NO: 1. The claims do not require that the proteins possesses any particular distinguishing feature, biologic activity, or conserved structure. Therefore, the claims are drawn to a genus of proteins that are defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in

the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemi chemical structure of the encompassed genus of proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written

description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a vaccine comprising an HIV envelope protein or a fragment thereof comprising certain amino acid sequences within residues of SEQ ID NO: 1. One of skilled in the art would doubt the efficacy of the claimed vaccine with the instant protein or any fragment thereof because there is no teaching that there would be divergent cross-reactivity between the different subgroups and clades *in vivo*. Lukashov et al. (AIDS Research and Human Retroviruses. 1996; 12 (10): 951-953) teaches the various sequences in the HIV envelope V3 region, which includes the instantly claimed phenotype, see the sequence alignment provided and reference sequence "SR923572" in Figure 1. Lukashov et al. sequences 44 individuals in this region and only one is found to have the instant sequence. Therefore, this sequence does not representative in a large number of subjects and the skilled artisan would doubt the cross-reactivity of the instant sequence with other serum samples derived from different strain of HIV. Therefore, the comparative neutralization of different sera with R2 and envelopes with other diverse phenotypes in example 4 of the disclosure is not indicative of the type of response to the protein once administered due to diverse variation of HIV sequences. Hypervariability of sequences among the different HIV strains is a well-recognized concern in the HIV art; see the teachings of Korber et al. (British Medical Bulletin. 2001; 58: 19-42) as a general review in the art. The teachings of Kelleher et al. (AIDS Research and Human Retroviruses. 1997; 13 (1): 29-

32) provide further evidence that the instant protein or fragments would not induce a protective immune response. Kelleher et al. teaches poor immune response following administration of a V3 peptide and an adjuvant to 24 individuals. The working examples do not provide evidence that the instant composition provides protection. There is currently no animal model for HIV, see the teachings of Klein et al. (Clinical Therapeutics. 2000; 22 (3): 295-314) on pages 304-305. Therefore, the neutralization assays in mice immunized with full-length R2 and R2 fragments in example 9 of the specification does not indicate the applicability to humans. The skilled artisan would be unable to predict the response or effectiveness of the instantly claimed protein. In conclusion, the instant specification does not address or remedy the concerns in the art.

Therefore, due to the lack of predictability in the HIV vaccine art, and the lack of data in the disclosure drawn to cross-neutralization among all of the hypervariable sequences among the various HIV strains, it is determined that undue experimentation would be required of the skilled artisan to make or use the instant vaccine to prevent or treat HIV infection.

Applicant argues that the envelope proteins in the working examples demonstrate that the antibodies are effective in inducing neutralizing antibodies against multiple strains of HIV *in vitro*. Applicant also cites a peer-reviewed journal publication of Zhang et al. and asserts that the data indicate that the instant protein is capable of generating a broadly cross-reactive response to multiple strains of HIV *in vitro*. Applicant also reminds the examiner that clinical data is not required to demonstrate enablement generation of neutralization of multiple HIV strains *in vitro*.

Applicant's arguments have been carefully considered, but are found unpersuasive. Although applicant has provided sufficient evidence demonstrating cross-reactive neutralizing capability of the protein *in vitro*, the claim is drawn to a vaccine. A vaccine is required to induce

active, protective immunity against a pathogen *in vivo*. There is no working example or guidance provided in the specification that remedies the lack of predictability or concerns of the skilled artisan, discussed above by Korber et al., Kelleher et al. and Klein et al., regarding the development of HIV vaccines. Therefore, it is maintained that the skilled artisan would be unable to formulate a vaccine composition comprising the instant protein without an undue amount of experimentation.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24 and 30 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sala et al. (Journal of Virology. 1994; 68 (8): 5280-5283). The amino acid residues of Sala et al. corresponding to the required amino acid residue position numbers recited in the claim is evidenced by the sequence alignment of SEQ ID NO: 1 with Sala et al. SPTREMBL_17; Accession No: Q78039; November, 1996; from J. Virol.; 68: 5280-5283.

Claims 24 and 30 are also rejected under 35 U.S.C. 102(b) as being clearly anticipated by the sequence alignment of Lukashov et al. (SPTREMBL_17 database; Accession No: Q69692; 1996; from AIDS Research and Human Retroviruses; 12: 951-953).

The claims are drawn to an isolated HIV envelope protein fragment of 13 to 100 amino acids in length comprising a proline at a position corresponding to amino acid residue 313, a methionine corresponding to amino acid residue 314 and a glutamine corresponding to amino

acid residue 325 of SEQ ID NO: 1 that induces neutralizing antibodies against multiple strains of HIV *in vitro*.

See the sequence alignment of Sala et al. or Lukashov et al. The references, in the alternative, clearly anticipate an HIV envelope protein fragment that is at least 13 amino acids in length comprising the required amino acid residues in the required position numbers of SEQ ID NO: 1. Therefore, because the protein fragments of Sala et al. or Lukashov et al. comprise the required structural features specified by the claims, the fragments of Sala et al. or Lukashov et al. also inherently possess the ability to produce antibodies against HIV-1 strains *in vitro*.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sala et al. or Lukashov et al. supra.

The claim is drawn to a recombinant HIV envelope protein comprising a proline at a position corresponding to amino acid residue 313, a methionine corresponding to amino acid residue 314 and a glutamine corresponding to amino acid residue 325 of SEQ ID NO: 1 that induces neutralizing antibodies against multiple strains of HIV *in vitro*.

See the teachings of Sala et al. or Lukashov et al. above. Although neither reference teach the entire glycoprotein, the amino acid sequence of the fragment taught by either reference renders the HIV envelope protein from which the sequence is derived, obvious. It would have

been prima facie obvious for one of ordinary skill in the art at the time the invention was made to isolate the HIV envelope protein to amplify specific regions within the protein or clone the HIV envelope into a vector for evaluation in various recombinant assays with a reasonable expectation for producing the claimed invention because the sequence parameters of the HIV envelope protein were well known at the time the invention was made. Additionally, since it is demonstrated that the protein fragment of Sala et al. or Lukashov et al. share identical amino acid requirements of instant recombinant protein, it is determined that an envelope protein comprising the sequence disclosed by Sala et al. or Lukashov et al. would also induce an immune response *in vitro*.

Claims 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sala et al. or Lukashov et al. supra as applied to claims 24 and 30 above, and further in view of Haynes (US 5,993,819).

The claims are drawn to an immunogenic composition and a method of generating antibodies in a mammal by administering an HIV envelope protein fragment comprising specific residues of SEQ ID NO: 1.

See the teachings of Sala et al. or Lukashov et al. above. Neither reference teaches the fragment in an immunogenic composition or inducing an immune response.

However, Haynes et al. clearly teach an HIV envelope glycoprotein comprises antigenic determinants recognized by B lymphocytes that induces antibodies against HIV. Haynes et al. also teach that the V3 region of HIV induce HIV antibodies and that 50% of HIV isolates at the time of the reference are similar to the MN isolate and that 80% of the HIV isolates in the US

share one of 4 most common sequences that induce cross-reactive HIV neutralizing antibodies, see column 2, lines 25-40.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer the protein fragments of Sala et al or Lukashov et al. to induce HIV antibodies in a subject. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the instant invention because Sala et al. or Lukashov et al. teach sequences of a portion of the V3 region of HIV and Haynes et al. teach that the V3 region induces HIV antibodies. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

***Allowable Subject Matter***

The prior art does not teach or suggest an HIV envelope protein comprising or consisting of SEQ ID NO: 1. Therefore, claims 2 and 23 are drawn to allowable subject matter.

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
March 7, 2003

JAMES HOUSEL 3/10/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600